Q9

35. The kit of claim 33 wherein said reaction tube further comprises a cap for facilitating disposal of biological waste.

Q10

38. The kit of claim 36 wherein said reaction tube further comprises a cap for facilitating disposal of biological waste.

Remarks

The present invention is directed towards a method and analytical device for the determination of the presence of free light chains (Bence Jones proteins), and classes thereof (kappa and lambda) in a untreated urine sample. The method and device allow the sample to react with an anti-free light chain antiserum reagent, where the presence of the free light chains is revealed by improved specific binding assay methods, including kits and devices utilizing chromatographically mobile specific binding reagents labeled with colloidal particles. Both sandwich and competitive assays are disclosed.

Rejections Under 35 U.S.C. § 112

The Examiner has rejected Claims 1-38 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 24 and 31 have been cancelled. Claims 1-3, 7-10, 12, 13, 15, 20, 21, 23, 26, 28, 29, 30, 35, 38 have been amended and obviate each of the Examiner's rejections under 35 U.S.C. 112.

In claim 1, the examiner has objected to the term "contacting" and taken the position that it relates to steps reciting the location of various pieces of the device. Applicant respectfully submits that "contacting" in claim 1, line 14, refers to the method step of "contacting" or positioning the conjugate pad in contact with the chromogenic test strip in a specific location. Figures 1, and 3 both show the placement of the conjugate pad in contact with the test strip.

Similarly, in claim1, line 17, "contacting" refers to the method step of placing the chromatographic test strip in contact with the absorbent pad in a specific location. Figures 1, and 3 both show the specific placement of the chromatographic test strip in contact with the absorbent pad.

Claim 1 has been further amended with respect to the control reaction site.

Claim 3 has been amended, and it is respectfully submitted that the claim is in proper Markush format. It is well known in the art that the analytes of interest to the present invention include (1) free and bound kappa light chains; (2) free and bound lambda light chains; (3) free kappa light chains; and (4) free lambda light chains. The Markush group has been rearranged to minimize confusion between Markush prose, and the species which incorporates the word "and."

Claim 6 has been amended and is now in proper Markush format.

Claim 7 has been amended and further put into proper Markush format.

Claim 8, and 9 has been amended to provide clarification.

Claim 10, 12, and 13 has been amended for clarification.

Applicant respectfully submits that claim 15 is in proper Markush format. Applicant submits that it is well known in the art that "free and bound kappa" refers to a species known in the art. The "and" in "free and bound" is part of the name of the species.

The Examiner for clarification as to what "free kappa chains" are being claimed, and whether these are free kappa chains of IgG. The Applicant respectfully submits that the free kappa chains refer to free kappa light chains, a type of Bence Jones protein.

The Applicant respectfully submits that claim 20 is now in proper Markush format. There is an inherent difficulty of trying to claim species which incorporate the word "and" into Markush format which requires a specific placement of the term "and". Appli-

cant respectfully submits that the chromogenic mobile specific antibody of claim 13 is selected from "conjugated anti-free and bound kappa antibody", and "conjugated anti-free and bound lambda antibody". Applicant has inserted a comma in claim 20 for clarification.

Applicant respectfully submits that claim 21 has been amended for clarification.

Applicant respectfully submits that claim 23 is in proper Markush format.

Claims 35 and 38 have been amended to provide antecedent support.

Rejections Under 35 U.S.C. § 102

The Examiner has rejected Claims 1, 2, 4, 5, 11-19, 24-27, 31 and 32 under 35 U.S.C. 102(b) as being anticipated by May. Applicant respectfully disagrees with the Examiner for the following reasons:

May discloses a device useful for example in pregnancy testing which comprises a hollow casing constructed of moisture-impervious solid material containing a dry porous carrier, for example nitrocellulose which communicates indirectly with the exterior of the casing by a bibulous sample receiving member. The sample-receiving member protrudes from the casing such that a liquid test sample can be applied to the receiving member and permeates there from to the porous carrier.

In order to anticipate a claim, the reference must teach each and every element of the claim. *See* MPEP 2131. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "

Claim 1, an independent claim from which claims 2, 4, 5, 11, and 12 depend, requires, among other limitations, the step of providing a conjugate pad. Claim 1 of the

applicant's invention requires the step of providing a conjugate pad. For example, Fig. 1a and 1b show conjugate pad (2). Applicants respectfully submit that this limitation of a conjugate pad is not disclosed, taught or suggested by May. Accordingly, claim 1, and every claim that depends upon claim 1 (including claims 2, 4, 5, 11, and 12), are not anticipated by the May reference.

With respect to claim 13, an independent claim from which claims 14, 15, 16, 17, 18, 19, and 25 depend, requires, among other limitations, a conjugate pad. Claim 13 requires a conjugate pad. Applicants respectfully submit that this limitation is not disclosed, taught or suggested by May. Accordingly, claim 13, and every claim that depends upon claim 13 (including claims 14, 15, 16, 17, 18, 19, and 25), are not anticipated by the May reference.

With respect to claim 26, an independent claim from which claims 27, 31 and 32 depend, this claim has been amended to require the analyte be selected from the group consisting of free light chains and classes thereof. Applicants respectfully submit that this added limitation is not disclosed, taught or suggested by May. Accordingly, claim 26, and every claim that depends upon claim 26 (including claims 27, 31 and 32), are not anticipated by the May reference.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected Claims 3, 6, 7, 8, 10, 20, 21,23, 28, and 29 under 35 U.S.C. 103 as obvious over May in view of Massaro. May is described above.

Massaro relates to a method of determining the presence of free light chains (Bence Jones protein) in a pretreated urine sample in which the sample is centrifuged and reacted with an anti-free light chain antiserum reagent, where the presence of the free light chains is revealed by increase in turbidity of the reacted sample. By comparison with the turbidity of calibrators having predetermined concentrations reacted with anti-free light chain antiserum, a quantitative analysis of the amount of free light chains

in the urine sample can be determined. A kit for performance of the analysis, including anti-free light chain antiserum reagent, calibrator, and reagent without antiserum, is also provided. In particular Massaro proposes a diagnostic method based on ascertainment of the concentration of light chains in the urine comprising the phases (a) centrifugation of the urine sample and separation of the overfloating, (b) addition to the sample of an anti free light chain antiserum reagent operating with an excess of antibodies, and (c) appraisal of turbidity of the reacted sample.

Applicant respectfully disagrees with the Examiner that claims 3, 6, 7, 8, 10, 20, 21,23, 28, and 29 are obvious for the following reasons:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See MPEP 2143.

First, the Examiner has correctly asserted that May differs from the instant invention in failing to teach the detection of analytes such as free and bound kappa and lambda chains of immunoglobins, and that Massaro does teach the detection of Bence Jones proteins in urine samples. However, Applicant respectfully disagrees with the Examiners position that Applicant's invention is obvious because there is no suggestion in either of the cited references to combine them nor would a skilled artisan have had a reasonable expectation of success in using a modified device in May to detect Bence Jones proteins, in light of Massaro. In order to be obvious, the teaching or suggestion to make the claimed combination *and* the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP 2143. Massaro teaches a multistep test for detecting Bence Jones Proteins by centrifuging and pre-treating urine. In Column 2,

Massaro teaches a diagnostic method based on ascertainment of the concentration of light chains in the urine comprising, among other things, centrifugation of the urine sample, and appraisal of turbidity of the reacted sample. Since Massaro teaches a multistep test for Bence Jones proteins by centrifuging and analyzing the turbidity of a liquid sample, there is no suggestion whatsoever to make the claimed combination of prior art references to arrive at the claimed invention.

In fact, a combination of May and Massaro would result in the urine sample being pretreated through centrifugation and the addition of antiserum reagent directly to the sample before being tested according to May. In contrast the claimed invention suggests no pretreatment of the urine sample, and the use of a conjugate pad.

The present invention describes the detection of Bence Jones Proteins using a chromatographic strip. No reasonable expectation of success should be inferred from the prior art references. In fact, Applicant respectfully submits that the Examiner is using improper hindsight reasoning to find the claimed invention obvious.

Second, the prior art references when combined fail to teach or suggest all of the claim limitations.

As discussed above, claim 1, an independent claim from which claims 3, 6, 7, 8, 10 depend, requires, among other limitations, the step of providing a conjugate pad. Nowhere does May or Massaro teach the step of providing a conjugate pad, as does the claimed invention. Since the prior art references fail to mention a conjugate pad, claims 3, 6, 7, 8, and 10 are not obvious.

As discussed above, claim 13, an independent claim from which claims 20, 21, and 23 depend, requires, among other limitations, a conjugate pad. Claim 13 requires a conjugate pad. Applicants respectfully submit that this limitation is not disclosed, taught or suggested by either May or Massaro. Accordingly, claim 13, and every claim

that depends upon claim 13 (including claims 20, 21, and 23), are not obvious in light of May or Massaro.

As discussed above, claim 26, an independent claim from which claims 28 and 29 depend, this claim has been amended to require the analyte be selected from the group consisting of free light chains and classes thereof. Applicants respectfully submit that this added limitation is not disclosed, taught or suggested by either May or Massaro for use in a test strip. Accordingly, claim 26, and every claim that depends upon claim 26 (including claims 28 and 29), are not obvious in light of May and Massaro.

The Examiner has further rejected Claims 9, 22, and 30 under 35 U.S.C. 103 as obvious over May in view of Massaro, and further in view of Brizgys. The Applicant respectfully submits that these dependent claims are not obvious because of the reasons stated above showing that the independent claims upon which claims 9, 22, and 30 depend are not obvious.

Brizgys relates to a test system useful in carrying out diagnostic assays. One component of the test system is an unblocked solid phase test carrier with a three dimensional configuration, impregnated with a first binding partner for analyte of interest. The second component of a binding agent containing a second binding partner coupled to an immediately visually determinable label, and a blocking agent. Protein A is shown as an example of a captured and labeled receptor.

Claim 9, is dependent upon claim 1 which requires, among other limitations, the step of providing a conjugate pad. Since Brizgys fails to teach the step of providing a conjugate pad, and claim 1 is not obvious for the reasons stated above, dependent claim 9 is not obvious.

Claim 22, is dependent upon claim 13, which requires, among other limitations, a conjugate pad. Claim 13 requires a conjugate pad. Since Brizgys fails to show a con-

jugate pad, and claim 13 is not obvious for the reasons stated above, dependent claim 22 is not obvious.

With respect to claim 30, dependant upon claim 26. Claim 26 has been amended to require the analyte be selected from the group consisting of free light chains and classes thereof. Applicants respectfully submit that this added limitation is not disclosed, taught or suggested by either May, Massaro, or Brizgys. Accordingly, claim 30 is not obvious.

The Examiner has further rejected Claims 33-38 under 35 U.S.C. 103 as obvious over May in view of Massaro, and further in view of Deutsch. The Applicant respectfully submits that these dependent claims are not obvious because of the reasons stated above showing that the independent claim 13 and 26 are not obvious.

Deutsch relates to a test device for determining a characteristic of a sample, particularly for determining substances in fluid samples. The device comprises a strip element which is composed of a material capable of transporting a developing fluid there along by capillarity and which has a portion at a predetermined location on the strip element for receiving the test sample and portions at predetermined locations on the strip element incorporated with reagent means for providing a detectable response sensitive to the characteristic under determination. The beginning end portion of the strip element is immersed in the developing fluid which, as a result, traverses the length of the strip element, thereby promoting appropriate contact between the test sample and the reagent means resulting in the disposition of a detectable response at a predetermined location on the strip element, which response is a function of the characteristic under determination.

The Examiner has correctly taken the position that the test tube in Deutsch is for holding developing liquid and not a urine sample, however, Applicants respectfully disagree that Deutsch renders the instant claims obvious.

In order to render the claims obvious, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See MPEP 2143. Claim 26 has been amended to require the analyte be selected from the group consisting of free light chains and classes thereof. Nowhere do any of the prior art references disclose this limitation as required by the claimed invention. Accordingly, since claim 26 is not obvious, those claims which depend upon claim 26 (claims 33, 34, 35) are not obvious.

In order to render the claims obvious, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See MPEP 2143. With respect to claim 13, an independent claim from which claims 36, 37, and 38 depend, requires, among other limitations, a conjugate pad. Claim 13 requires a conjugate pad. Applicants respectfully submit that this limitation is not disclosed, taught or suggested by any of the prior art references. Accordingly, claims 36, 37, and 38 are not obvious.

Claims 24 and 31 have been cancelled. Claims 1-3, 7-10, 12, 13, 15, 20, 21, 23, 26, 28, 29, 30, 35, 38 have been amended. It is respectfully submitted that claims 1-40, all of the claims remaining in the application, are in order for allowance, and early notice to that effect is respectfully requested.

The Examiner is invited to call Michael Krenicky at (203) 324-6155 if the Examiner has any questions about this invention or response.

Respectfully submitted,

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Version with Markings to Show Changes Made

1. A method for determining the presence of [an analyte] Bence Jones Proteins in urine sample, comprising the steps of:

providing a conjugate pad comprising a chromogenic mobile specific binding partner for [an] binding to analyte;

providing a chromatographic test strip comprising a matrix through which a urine test sample can flow by capillarity wherein said chromatographic test strip comprises at lease two reaction sites;

a first reaction site comprising a first immobilized specific binding reagent capable of immobilizing said chromogenic mobile specific binding partner in relation to the presence of the analyte in the urine sample; [and]

a control reaction site comprising a second immobilized specific binding reagent capable of immobilizing said chromogenic mobile specific binding partner;

contacting said conjugate pad to said chromatographic test strip such that said first reaction site lies between said conjugate pad and said control reaction site;

contacting said chromatographic test strip with an absorbent pad such that said absorbent pad is positioned opposite said conjugate pad and such that both said first reaction site and control reaction site lie in-between said conjugate pad and said absorbent pad;

developing said chromatographic test strip by applying urine sample suspected of containing said analyte thereto thereby allowing the same to contact said chromogenic mobile specific binding partner to form an analyte/chromogenic mobile specific binding partner complex whereby capillarity carries the urine test sample along the strip to the first reaction site containing said first immobilized specific binding reagent and said control reaction site comprising said second immobilized specific binding partner;

determining the presence of analyte in the urine test sample by [detecting the presence of chromogenic complex at] viewing said first reaction site;

determining if migration has occurred by detecting the presence of [chromogenic complex] analyte/chromogenic mobile specific binding partner complex at said control reaction site; wherein detection may be made by observation of color at the control reaction site.

2. The method of claim 1 wherein the step of providing a chromatographic test strip further comprises [comprising] providing a second reaction site positioned in-between said first reaction site and said control reaction site wherein said second reaction site is capable of immobilizing said chromogenic mobile specific binding partner in relation to the presence of said analyte in said urine, wherein said analyte is selected from the group consisting of free and bound kappa light chains, and free and bound lambda light chains [whole antibody in said urine].

3. The method of claim 1 wherein said analyte is selected [form] from the group consisting of free and bound lambda light chains, free and bound kappa light chains, free [and bound] kappa light chains, and free lambda light chains[, and free and bound lambda].

6. The method of claim 1 wherein said chromogenic mobile specific binding partner is selected from the group consisting of conjugated anti-free and bound kappa light chain antibody, and conjugated anti-free and bound lambda light chain antibody.

7. The method of claim 1 wherein said first immobilized specific binding reagent is selected from the group consisting of free and bound kappa light chains, [free and bound kappa,] free and bound lambda light chains, free kappa light chains, and free [and bound] lambda light chains [for performing a competitive analysis].

8. The method of claim 1 wherein said first immobilized specific binding reagent is selected from the group consisting of anti-free kappa light chain antibody, [and] anti-free lambda light chain antibody, anti- free and bound kappa light chain antibody, and anti-free and bound light lambda light chain antibody.

9. The method of claim 1 wherein said second immobilized specific binding reagent is Protein A [for the detection of immunochemicals].

10. The method of claim 1 further comprising providing a chromatographic test strip [wherein said] further comprising a second reaction site, wherein said second reaction site further comprises a [second] third immobilized specific binding reagent selected from the group consisting of anti-free and bound kappa light chain antibody, anti free kappa light chain antibody, anti-free lambda light chain antibody, and anti-free and bound lambda light chain antibody [for the determination of the presence of whole antibody].

12. The method of claim 1 wherein the step of determining the presence of analyte in urine further comprises visualization of said first and said control reaction site, wherein the absence of band formation at said first reaction site indicates a positive result and the visualization of a band at said first reaction site indicates a negative result [and wherein the visualization of band formation at said control reaction site indicates that the test has worked in competitive assay].

13. A device for the detection of analyte in urine comprising:

a conjugate pad said conjugate pad comprising a chromogenic mobile specific binding partner capable of binding to [an] analytes;

a chromatographic test strip comprising a matrix through which urine can pass by capillarity carrying said mobile specific binding partner and said analyte, wherein said chromatographic test strip comprises three reaction sites,

a first reaction site comprising [an] a first immobilized specific binding reagent capable of immobilizing said chromogenic mobile specific binding partner [in relation to the presence of the] bound to a first analyte in the urine sample,

a second reaction site comprising a second immobilizing specific binding reagent capable of immobilizing said chromogenic mobile specific binding partner [in relation to the presence of the] bound to second analyte in the urine sample,

a third control reaction site comprising a third immobilizing specific binding partner capable of immobilizing said mobile specific binding partner [in relation to the capillary action transporting said chromogenic mobile specific binding partner through said chromatographic test strip];

an absorbent pad disposed upon said chromatographic test strip such that said absorbent pad is positioned opposite said conjugate pad and such that said first reaction site, second reaction site, and said third reaction site lie in-between said conjugate pad and said absorbent pad.

15. The device of claim 13 wherein said first analyte is selected form the group consisting of free kappa light chains, free and bound kappa light chains, free lambda light chains, and free and bound lambda light chains.

20. The device of claim 13 wherein said chromogenic mobile specific binding partner [antibody] is selected from the group consisting of conjugated anti-free and bound kappa light chain antibody, [and] conjugated anti-free and bound lambda light chain antibody, conjugated anti-free kappa light chain antibody, and conjugated anti-free lambda light chain antibody.

21. The device of claim 13 wherein said first immobilized specific binding reagent is selected from the group consisting of anti-free kappa light chain antibody and anti-free lambda light chain antibody.

23. The device of claim 13 wherein said second immobilizing specific binding reagent is selected from the group consisting of anti-free and bound kappa light chain antibody, and anti-free and bound lambda light chain antibody for the determination of the presence of whole antibody.

26. A test strip for the determination of an analyte in urine comprising:

a backing member;

a chromatographic test strip disposed upon said backing member said chromatographic test strip comprising a matrix through which a urine sample can flow by capillarity wherein said chromatographic test strip comprises at lease two reaction sites,

a first reaction site comprising [an] a first immobilized specific binding reagent capable of immobilizing a chromogenic mobile specific binding partner bound to said [in relation to the presence of the] analyte in the urine sample; and

a second reaction site comprising a second immobilized specific binding reagent capable of immobilizing said chromogenic mobile specific binding partner; wherein said analyte is selected from the group consisting of free light chains and classes thereof.

28. The test strip of claim 26 wherein said chromogenic mobile specific binding partner is selected from the group consisting of anti-free kappa light chain antibody, anti-free and bound kappa light chain antibody, anti-free lambda light chain antibody, and anti-free and bound lambda light chain antibody.

29. The test strip of claim 26 wherein said first immobilized specific binding reagent is selected from the group consisting of free kappa light chains, free and bound kappa light chains, free lambda light chains, and free and bound lambda light chains.

30. The test strip of claim 26 wherein said second immobilized specific binding reagent is Protein A.

35. The kit of claim 33 wherein said reaction tube further comprises a cap for facilitating disposal of biological waste.

38. The kit of claim 36 wherein said reaction tube further comprises a cap for facilitating disposal of biological waste.